Xenopus (SEQ ID NO: 13) GXII $sPLA_2$s (sequences were deduced from the alignment of different ESTs and from the BAC clone). For some $sPLA_2$s, the XX residues indicate that the sequence is partial. The *Arrowhead* indicates the predicted signal peptide cleavage site (32). The active site region containing catalytic site residues that are found in all $sPLA_2$s, and the putative Ca^{2+} binding segment (SEQ ID NO: 8) GCGSP are indicated. The level of identity between the mature protein sequence of hGXII and other GXII $sPLA_2$s is shown. Panel B shows alignment of the Ca^{2+}-binding and active site regions of hGXII (SEQ ID NO: 18) with a representative member of the four other structural classes of $sPLA_2$s (hGIB (SEQ ID NO: 14) for GI/II/V/X $sPLA_2$s, hGIII (SEQ ID NO: 15) for GIII $sPLA_2$s, Conodipine-M (SEQ ID NO: 16) for GIX $sPLA_2$, and Rice II (SEQ ID NO: 17) for GXI $sPLA_2$s).

A2

Please replace the paragraph 0015 (last paragraph bridging pages 5 and 6) with the following:

[0015] Thus, the invention concerns a novel mammalian secreted group XII $sPLA_2$ wherein said enzyme contains a potential Ca^{2+} binding segment (SEQ ID NO: 8) GCGSP. The invention concerns more particularly a mammalian secreted group XII $sPLA_2$ comprising the sequence of amino acids under SEQ ID NO: 2. More particularly, the mammalian secreted group XII $sPLA_2$ is a human secreted group XII $sPLA_2$.

A3

Please replace the 0034 (last paragraph bridging pages 14 and 15) with the following:

[0034] A blastp search with the amino acid sequence of hGXII $sPLA_2$ against the protein databases stored at the National Center for Biotechnology reveals matches to a variety of $sPLA_2$s from mammals, *C. elegans*, plants and animal venoms, suggesting that this

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protein belongs to the $sPLA_2$ family. The homology however appears to be weak (< 35% identity with blast scores lower than 35) and restricted to a short stretch of less than 60 amino acid residues containing the active site domain and the HD catalytic diad, indicating that the hGXII $sPLA_2$ is unique among all known $sPLA_2$s (Fig. 1B). The histidine of HD is thought to function as a general base to deprotonate a water molecule as it attacks the substrate ester carbonyl carbon, and the ß-carboxyl group of the adjacent aspartate coordinates directly to the catalytic Ca^{2+} cofactor (6,33). Except for 3 cysteines in the active site consensus sequence (SEQ ID NO: 9) CCXXHDXC which match those of other groups of $sPLA_2$s, the location of the other 11 cysteines residues in hGXII is distinct from that of other $sPLA_2$s (Fig. 1B). Since the structural arrangement of disulfides has been the main basis for designating the different $sPLA_2$ group numbers, the naming of the new $sPLA_2$ as hGXII seems appropriate.

A4

Please replace paragraph 0035 (the paragraph bridging pages 15 and 16) with the following:

[0035] The homology between hGXII and all known $sPLA_2$s is so low that it is difficult to find the Ca^{2+} binding loop, which is usually highly conserved and provides 3 of the 4 amino acid ligands for the catalytic Ca^{2+} (34). All mammalian group I, II, V, and X $sPLA_2$s contain 19 amino acid residues between the most N-terminal residue that serves as a ligand to the active site Ca^{2+} (i.e. His-27 of hGIIA) and the catalytic histidine (i.e. His-47 of hGIIA). In contrast, the corresponding distances for hGIII and plant GXI $sPLA_2$s are 25 and 23 residues, respectively, hGXII contains a potential Ca^{2+} binding segment (SEQ ID NO: 8) GCGSP with 23 residues between the N-terminal glycine and the putative catalytic

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histidine as shown in Fig. 1. This segment is perfectly conserved among all of the GXII proteins found in gene databases. The x-ray structures of groups I, II, and III $sPLA_2$s reveal that the Ca^{2+} loop contains the consensus segment $X_1CG_1X_2G_2$. The backbone carbonyl oxygens of residues X_1, G_1, and G_2 coordinate to Ca^{2+}, and the backbone NH of G_1 is proposed to donate a hydrogen bond to the carbonyl oxygen of the enzyme-susceptible substrate ester (33,35). The fact that this residue is glycine in catalytically active $sPLA_2$s and that mutating this residue to serine lowers catalytic activity by about 10- to 20-fold (35) argues that steric bulk is poorly tolerated at this position. The putative Ca^{2+}-coordinating segment of hGXII shown in Fig. 1B fits the consensus sequence of other $sPLA_2$s with the exception that G_2 is a proline in hGXII. The prediction based on examination of the x-ray structures of $sPLA_2$s is that the hGXII Ca^{2+} binding segment should be functional. It contains G_1, and the backbone carbonyl of the C-terminal proline can coordinate to Ca^{2+} since its three extra methylenes, compared to glycine, are sterically allowed because of the location of this residue on the enzyme's surface away from the substrate binding cavity. Interestingly, $sPLA_2$ isozymes with relatively low $sPLA_2$ activity from the venom of the banded krait also contain proline in place of G_2 (36).